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Concurrent chemoradiotherapy with cisplatin or cetuximab for locally advanced head and neck squamous cell carcinomas: Does human papilloma virus play a role?

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SUMMARY

Objectives: The optimal concurrent regimen, chemoradiotherapy (CRT) or bioradiotherapy (BRT), in locally advanced head and neck squamous cell carcinoma (LAHNSCC) remains controversial, especially in human papilloma virus-associated patients.
Material and methods: Data of 265 patients with LAHNSCC treated with CRT (cisplatin, 100 mg/m^2 every 3 weeks, $n = 194$) or BRT (weekly cetuximab, $n = 71$), including 119 patients with known HPV/p16 status were analyzed.
Results: Median follow-up was 54.5 months. The 5-year progression-free survival (PFS) and locoregional control (LRC) were 51.7% vs. 36.9% ($p = 0.01$) and 74.2% vs. 51.2% ($p = 0.002$), both in favor of CRT. Multivariate analysis adjusted for p16 status continued to show improved outcomes (PFS and LRC) for CRT. The 5-year LRC was significantly better with CRT vs. BRT both in the p16+ subgroup ($p = 0.01$) and in p16− or unknown subgroup ($p = 0.02$), and 5-year PFS was of non-significant trend of improvement with CRT vs. BRT in both subgroups ($p = 0.07$ in p16+ and $p = 0.09$ in p16− or unknown, respectively). In the subset of oropharyngeal cancer patients with HPV/p16 status available ($n = 88$), MVA after adjusted for other clinical co-variates showed a non-significant trend of improvement of LRC with CRT compared with BRT (HR = 0.4, 95%CI, 0.1–1.0; $p = 0.06$).
Conclusion: Our long-term results suggested better outcomes in LAHNSCC patients receiving concurrent cisplatin over cetuximab regardless of HPV/p16 status.

Introduction

The current standard of care for patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) is concurrent chemoradiotherapy (CRT) [1]. The use of high-dose (100 mg/m^2 every 3 weeks) cisplatin concurrent with radiotherapy (RT) is considered a standard CRT regimen [2]. However, CRT has been associated with frequent severe acute and late toxicities [3], and less toxic regimens have been investigated.

Combination of RT with agents targeting the epidermal growth factor receptor (EGFR) is one alternative for patients who are ineligible for CRT because of older age or comorbidities [4]. The phase III randomized trial reported by Bonner et al. showed a benefit in LRC and OS in favor of concurrent bioradiotherapy (BRT) with cetuximab compared to RT alone [5]. In a reanalysis of the trial, the benefit of survival outcomes with BRT vs. RT persisted regardless of p16 or HPV status [6]. However, published results of phase III randomized trials which directly comparing cisplatin-based CRT and cetuximab-based BRT are still awaited, and a fortiori in patients of LAHNSCC with known human papilloma virus (HPV) status.

HPV status has been established as an important favorable prognostic factor in the locally advanced setting [7]. In the recent years there has been a growing interest in increasing the benefit/risk ratio in this population. While the efficacy of BRT compared to CRT is controversial, the utilization of BRT to treat the prognostically favorable HPV positive subsets has been suggested.

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Our previously published results of definitive radiotherapy showed increased outcomes with CRT over BRT in LAHNSCC [8]. Here, we investigate whether the benefit of concomitant cisplatin over cetuximab persist when taking into account the critical independent prognostic variable HPV status.

Materials and methods

Pathology

HPV status was determined by p16 expression staining with immunohistochemistry in 119 (45%) patients. We considered p16 as positive when nuclear staining was ⩾75–80% of cells. Cytoplasmic only staining was considered as negative.

Patients

From March 2006 to October 2012, 597 consecutive patients with newly diagnosed squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx registered in the head and neck cancer database at Gustave Roussy were treated with definitive CRT or BRT with curative intent. Approval for the study was obtained from the head and neck clinical research and ethics committee. Written informed consent was obtained from each patient. Detailed patients exclusion criteria as well as the final baseline and tumor characteristics of 265 patients have been previously published [8] and are reviewed in Table 1, with additional information of HPV/p16 status.

The CRT and BRT groups were well balanced except that patients receiving BRT had more pre-existing conditions (Charlson

Table 1
Baseline patient clinical characteristics and treatments.

Characteristics	Whole population (n = 265)				Oropharyngeal HPV/p16 sub-cohort (n = 88)		
	Overall n (%)	CRT n (%)	BRT n (%)	p	CRT n (%)	BRT n (%)	p
Total	265 (100)	194 (100)	71 (100)		63 (100)	25 (100)	
Median age (range, years)	58 (36–81)	58 (36–79)	60 (42–81)	0.001	58(38–79)	59(44–81)	0.1
Gender				0.7			1.0
Male	210 (79)	155 (80)	55 (77)		50 (79)	20 (80)	
Female	55 (21)	39 (20)	16 (23)		13 (21)	5 (20)	
Sublocalization				0.9			
Oral cavity	11 (4)	8 (4)	3 (4)				
Oropharynx	182 (69)	136 (70)	46 (65)				
Hypopharynx	33 (12)	21 (11)	12 (17)				
Larynx	39 (15)	29 (15)	10 (14)				
PS (ECOG)				0.7			0.8
0	202 (76)	149 (77)	53 (75)		48 (76)	18 (72)	
⩾1	63 (24)	45 (23)	18 (25)		15 (24)	7 (28)	
Charlson index				0.01			0.05
0	117 (44)	95 (49)	22 (31)		31 (49)	8 (32)	
1	73 (28)	54 (28)	19 (27)		20 (32)	6 (24)	
⩾2	75 (28)	45 (23)	30 (42)		12 (19)	11 (44)	
Alcohol status				0.9			0.3
Never	98 (37)	71 (37)	27 (38)		29 (46)	8 (32)	
Former	76 (29)	55 (28)	21 (30)		17 (27)	11 (44)	
Current	91 (34)	68 (35)	23 (32)		17 (27)	6 (24)	
Tobacco status				0.5			0.8
Never	49 (18)	39 (20)	10 (14)		19 (30)	6 (24)	
Former	114 (43)	82 (43)	32 (45)		28 (44)	11 (44)	
Current	102 (38)	73 (38)	29 (41)		16 (25)	8 (32)	
T classification				0.6			0.3
1–2	110 (42)	83 (43)	27 (38)		23 (37)	5 (40)	
3	85 (32)	63 (32)	22 (31)		25 (40)	11 (44)	
4	70 (26)	48 (25)	22 (31)		15 (24)	9 (36)	
N classification				0.06			0.2
0	65 (25)	41 (21)	24 (34)		10 (16)	9 (36)	
1	49 (19)	33 (17)	16 (23)		13 (21)	4 (16)	
2	134 (50)	106 (55)	28 (39)		37 (59)	11 (44)	
3	17 (6)	14 (7)	3 (4)		3 (5)	1 (4)	
Overall stage				0.3			0.7
I–II	28 (11)	18 (9)	10 (14)		2 (3)	0 (0)	
III	65 (25)	45 (23)	20 (28)		17 (27)	7 (28)	
IV	172 (65)	131 (68)	41 (58)		44 (70)	18 (72)	
Radiotherapy							
Median dose (Gy)	70 (12–75)	70 (12–75)	70 (36–75)	0.1	70(56–75)	70(64–70)	0.2
Median number of fractions	35 (6–36)	35 (6–35)	35 (18–36)	0.2	35(25–35)	35(26–36)	0.9
Median fractionation[a]	2(2–2.5)	2(2–2.35)	2 (2–2.5)	0.4	2(2–2.33)	2(2–2.5)	0.1
Median duration (days)[a]	49 (4–70)	49 (4–70)	49 (24–60)	0.2	49(37–70)	49(22–60)	0.9
IMRT	59 (23)	44 (23)	15 (21)	0.8	18(45)	5(20)	0.6
HPV				0.01			0.01
p16+	46 (17)	39 (20)	7 (10)		39 (62)	7 (28)	
p16−	73 (28)	44 (23)	29 (41)		24 (38)	18 (72)	
p16 unknown	146 (55)	111 (57)	35 (49)		/	/	

CRT: chemoradiotherapy with concurrent cisplatin; BRT: bioradiotherapy with concurrent cetuximab; IMRT: intensity-modulated radiotherapy; PS: performance status; ECOG: Eastern Cooperative Oncology Group.

[a] Patients treated with accelerated fractionated RT in the BRT group were excluded from this analysis.